Evaluating the Treatment with Favipiravir in Patients Infected by COVID-19: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: Considering the results of studies and the potential of using favipiravir treatment of COVID-19, reviewing the results of clinical trial studies and summarizing the results are of great importance. It may be possible to use favipiravir extensively in the future. Therefore, the purpose of the present systematic review and meta-analysis was to evaluate the improvement rates of favipiravir treatment in patients with COVID-19.

Materials and methods: From the electronic databases, PubMed, Cochrane Library, Embase, ISI have been used to perform systematic literature between 2010 and 2020. Therefore, a software program (Endnote X8) has been utilized for managing electronic titles. Searches were performed with mesh terms. The odds ratio between the two groups (Favipiravir and control) with a 95% confidence interval was calculated. Random effects were used to deal with potential heterogeneity, and I2 showed heterogeneity. The Meta-analysis and forest plots have been evaluated using a software program available in the market (i.e., Comprehensive Meta-Analysis Stata V16).

Results: According to the research design, 186 potentially important research abstracts and titles have been discovered in our electronic searches. Finally, two papers remained in agreement with our inclusion criteria required. Statistically, a significant difference observed between improvement rates of the Favipiravir group and control group (p=0.01).

Conclusion: Positive effect and improvement rates of favipiravir VS control groups observed to treat patients with COVID-19.

1. Introduction

Since the advent of COVID-19 in Wuhan, China, in December 2019[1] the virus has spread rapidly throughout China and many other countries and is still applying.[11] Early studies reported transmitted from animals to humans, but studies have illustrated human-to-human transmission of the COVID-19 through droplets or direct contact.[2, 3] So far, the 2019-nCoV has affected more than 14,508,892 total confirmed cases (total deaths, 606,206 cases) according to a new report in global statistics of COVID-19 by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (July 20, 2020).[15] It has been reported that the asymptomatic incubation period of the virus is between 2 and 14 days. However, in some studies, the incubation period has been reported to be up to 24 days.[15] Fever, tiredness, dry cough, and shortness of breath are the most common symptoms of COVID-19. Less common symptoms are aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, a rash on the skin, or discoloration of fingers or toes.[6] More than 80% of patients showed mild symptoms that may not increase the number of undiagnosed cases; these people are called carriers.[17] If the hospital is aggravated, it can lead to pneumonia, kidney failure, and even death. According to the WHO report, the case fatality ratio (CFR) is estimated to be over 4.5%. A cough or sneezing by a carrier can spread SARS-CoV-2 within a radius of about 6 ft. So social distance is said to minimize the spread of the disease in the community.[8] Due to the high prevalence of COVID-19 and its mortality rate, its treatment is limited, and new treatment options need to be provided. Still, due to little evidence in this field, treatment options should be developed over time. The use of existing drugs can provide an immediate treatment opportunity.[19] However, researchers now trying globally used drugs for the treatment of COVID-19, such as antimalarial hydroxychloroquine, antiretrovirals...
lopinavir/ritonavir and darunavir/ritonavir, and influenza drugs oseltamivir, remdesivir, and favipiravir.10, 11 To date, none of the treatments for COVID-19 have been definitively approved. Studies have shown that one of these treatment options that may be effective in treating COVID-19 is RNA polymerase inhibitor favipiravir, which is designed to treat influenza, Ebola, and other diseases.12 Another study also confirmed that favipiravir leads to a significantly faster recovery rate in patients with COVID-19.13 Considering the results of studies and the potential of using favipiravir in the treatment of COVID-19, reviewing the results of clinical trial studies and summarizing the results is of great importance. It may be possible to use favipiravir extensively in the future. Therefore, the purpose of the present systematic review and meta-analysis was to evaluate the improvement rates of favipiravir treatment in patients with COVID-19.

2. Materials and methods

Search strategy

From the electronic databases, PubMed, Cochrane Library, Embase, ISI have been used to perform systematic literature between 2010 and 2020. Therefore, a software program (Endnote X8) has been utilized for managing electronic titles. Searches were performed with mesh terms: ("favipiravir" [Supplementary Concept]) AND "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept]) AND "Safety" [Mesh] OR "Contraceptive Effectiveness" [Mesh].

This systematic review has been conducted based on the key consideration of the PRISMA14 and PICO or PECO strategy (Table 1).

Selection criteria

Inclusion criteria

1. Randomized controlled trials studies, controlled clinical trials, and prospective and retrospective cohort studies, Open-Label Control Studies.
2. Treatment of Favipiravir.
3. Success rate/ failure rate/ survival rate.
5. No country or language restrictions.

Exclusion criteria

1. In vitro studies, case studies, case reports, and reviews.

Table 1. PICO OR PECO strategy.

<table>
<thead>
<tr>
<th>PICO OR PECO strategy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>Population/ Patient: Patients with COVID-19</td>
</tr>
<tr>
<td>E</td>
<td>Exposure/ Intervention: Favipiravir treatment</td>
</tr>
<tr>
<td>C</td>
<td>Comparison: Favipiravir vs. control group</td>
</tr>
<tr>
<td>O</td>
<td>Outcome: success rate and safety of clinical of Favipiravir</td>
</tr>
</tbody>
</table>

Data Extraction and method of analysis

The data have been extracted from the research included regarding the study, years, study design, Favipiravir, control group, mean/ range of age and Onset symptoms. The quality of the studies included was assessed using the Cochrane Collaboration’s tool.15 The scale scores for low risk were 1 and for High and unclear risk was 0. Scale scores range from 0 to 6. A higher score means higher quality. For Data extraction, two reviewers blind and independently extracted data from the abstract and full text of studies included.

Moreover, the Odds ratio between two groups (Favipiravir and control) with a 95% confidence interval (CI), fixed-effect model, and Mantel-Haenszel method were calculated. Random effects were used to deal with potential heterogeneity, and I2 showed heterogeneity. The Meta-analysis and forest plots have been evaluated using a software program available in the market (i.e., Comprehensive Meta-Analysis Stata V16).

3. Results

According to the research design, 186 potentially important research abstracts and titles have been discovered in our electronic searches. In the first phase of the study selection, 156 research has been about the topics and abstracts. Therefore, we thoroughly assessed the complete full-text papers of the rest 28 studies in the second stage to exclude 26 publications due to the lack of the defined inclusion criteria. Then, TWO papers remained in agreement with our inclusion criteria required (Figure 1). Table 2 reports the individual studies in this meta-analysis.

Figure 1. Study Attrition.
Sample size

Therefore, two studies (Randomized controlled trial) have been included. The Number of Patients in the Favipiravir group was 73 male and 78 female, 151 Patients with COVID-19. In the control group were 72 males and 93 females, a total of 165. The mean age in the Favipiravir group and control group was 45 years (Table 2).

Onset symptoms

All the baseline characteristics such as Fever, Cough, Headache, myalgia, Chill, Diarrhea and sore throat in Favipiravir group and control group report in table 3.

Improvement rates

The odds ratio of clinical recovery rate was 0.63 (OR 0.63 CI95% 0.16, 1.10 P=0.01) among 2 RCT studies and heterogeneity found (I² = 76.05%; P =0.04). This result showed a statistically significant difference between the Favipiravir group and control group (p=0.01) (Figure 2).

Bias assessment

According to Cochrane Collaboration's tool, two studies had a total score of 5/6. This outcome showed a low risk of bias in all studies and high-quality assessment (Table 4).

### Table 2. Studies were selected for systematic review and meta-analysis.

<table>
<thead>
<tr>
<th>Study. Year</th>
<th>Design</th>
<th>Number of Patients</th>
<th>Mean/Range of age</th>
<th>Favipiravir</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Cai et al. 2020 [16]</td>
<td>CT</td>
<td>80</td>
<td>43 (35.5–59)</td>
<td>49 (36–61)</td>
<td>Favipiravir: Dose: 1600 mg twice daily on Day 1 Dose: 600 mg twice daily on Days 2–14</td>
</tr>
<tr>
<td>Chen et al. 2020 [13]</td>
<td>RCT</td>
<td>236</td>
<td>47</td>
<td>41</td>
<td>Favipiravir: Dose: 1600 mg twice daily on Day 1 Dose: 600 mg twice a day on Days 2–14</td>
</tr>
</tbody>
</table>


### Table 3. Baseline Onset symptoms.

<table>
<thead>
<tr>
<th>R</th>
<th>Fever</th>
<th>Cough</th>
<th>Headache/myalgia</th>
<th>Chill</th>
<th>Diarrhea</th>
<th>Stuffy nose/sore throat</th>
</tr>
</thead>
<tbody>
<tr>
<td>[16]</td>
<td>22 (62.9%)</td>
<td>37 (82.2%)</td>
<td>12 (34.3%)</td>
<td>10 (22.2%)</td>
<td>5 (11.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>3 (8.6%)</td>
<td>1 (2.2%)</td>
<td>1 (2.9%)</td>
<td>0 (0%)</td>
<td>6 (17.1%)</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>[13]</td>
<td>64 (55.17)</td>
<td>61 (50.83)</td>
<td>70 (60.34)</td>
<td>64 (53.33)</td>
<td>2 (1.72)</td>
<td>3 (2.50)</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>22 (18.97)</td>
<td>15 (12.50)</td>
<td>9 (7.76)</td>
<td>17 (14.17)</td>
</tr>
</tbody>
</table>


### Table 4. Risk of bias according to Cochrane Collaboration's tool.

<table>
<thead>
<tr>
<th>Study. Year</th>
<th>Random sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Total score</th>
</tr>
</thead>
</table>
4. Discussion

Favipiravir (brand name: Avigan) is a drug developed by FUJIFILM Toyama Chemical Co., Ltd. (Japan). In 2014, it was reported by Fujifilm Toyama Chemical to neuraminidase inhibitors and treatment of influenza. Favipiravir has also been used to treat infections caused by RNA viruses such as Ebola, norovirus, and influenza. Recent studies have shown that favipiravir can be used to treat SARS-CoV-2 that is a single-stranded RNA virus. An in vitro study reported ribavirin, favipiravir, penciclovir, nafamostat, remdesivir, nitazoxanide, chloroquine are anti-SARS-CoV-2 medicines. Clinical trial studies have shown that patients' treatment with favipiravir showed a superior improvement rate (71.43%) than patients' treatment with umifenovir. Based on repeated findings and searches, eight studies have been performed to evaluate the effect of favipiravir anti-SARS-CoV-2. These studies include the evaluation of non-randomized and randomized controlled trials. In the present meta-analysis, only two clinical trials were included, a control group to compare the experimental group. The present systematic review and Meta-analysis findings show favipiravir have high improvement rates VS other medicines. Wu et al. in an updated review of drugs treating COVID-19, reported favipiravir to treatment COVID-19. Also, Arab-Zozani et al. determine the safety and effectiveness of favipiravir treatment of coronavirus. In this study, No RCT studies have been reported, no meta-analysis of results has been reported, and no comprehensive results have been reported. Another review by ilkington et al. determined favipiravir's safety; the result reported that favipiravir showed a favorable safety profile. Evidence suggests that the short-term use of favipiravir showed safety and tolerability. According to the findings, the use of favipiravir seems to be an effective treatment of COVID-19. However, to confirm these outcomes, more RCT studies with a high sample size and follow-up period are needed.

5. Conclusion

The present study shows a positive effect of favipiravir VS control groups to treat patients with COVID-19. Favipiravir is currently conducting clinical trials to evaluate its effectiveness and Immunity treatment of COVID-19. To achieve a more accurate outcome. It is hoped that the present study results can help assess the clinical recovery and efficacy of Favipiravir to treat patients with COVID-19 vs. other drugs and physicians selecting better treatment.

Conflict of Interest

The authors declared that there is no conflict of interest.

Acknowledgments

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